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Comparative dissolution study of drug and inert isomalt based core material from layered pellets

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ABSTRACT

Layered and coated pellets were formulated to control the release of the diclofenac sodium selected as model drug. A highly water soluble isomalt inert pellet core material was used to osmotically modulate the drug release through the swellable polyvinyl acetate coating layer. Image analysis was applied to determine the shape parameters and the swelling behavior of the pellets. UV-spectroscopy and liquid chromatography with refractive index detection were applied to measure the concentration of the model drug and the core materials. Simultaneous dissolution of both the diclofenac sodium and isomalt was observed. Relationship was found between the dissolution profile of the drug and the core material which linear correlation was independent on the coating level. The latter enables the modulation of drug release beside the permeability control of the swelled coating polymer.

1. Introduction

There is a growing interest toward the application of sugar substitutes (polyols, polyalcohols) as excipients for pharmaceutical formulations. The motivation for this interest is the recognition of their multiple potential health benefits. They are well tolerated [1–3] and have a reduced calorie content. Moreover they are suitable for patenient groups like diabetics and those suffering from lactose intolerance [4]. Their natural tasting sweetness and non-cariogenic (tooth-friendly) characteristics are improving the application of the sugar substitutes for the pharmaceutical formulation. A lot of polyols have shown good compactability and can be used in direct compression for the manufactures of tablets. They have a pleasant taste and excellent mouth feel [5]. Coated pellets based on sugar substitute cores are able to decrease the vulnerability of the dissolution kinetics to the changes in the osmotic environment [6]. In coated formulations polyols are able to increase the dissolution rate through the membranes in two ways. The presence of water-soluble polyols in the coating layer have a pore-forming effect and increase the permeability of the membrane [7] since in the core of the coated formulations these excipients increase the osmotic pressure resulting into increased water penetration through the coating layer [8–10]. Isomalt is a water soluble crystalline sugar alcohol. The pharmaceutical grades of isomalt (galenIQ) are mixtures of two disaccharide, the 1-*O*-α-D-glucopyranosyl-D-mannitol (GPM) dihydrate and 6-*O*-α-D-glucopyranosyl-D-sorbitol (GPS) in 1:1 or 1:3 molar ratio. The commercial grade galenIQ™ 980 is a pellet core material and in our previous study we reported the successful production of inert pellet cores via extrusion/spheronization using milled isomalt [11]. Polymeric film coating is commonly applied in the preparation of modified release dosage forms [12–14]. The drug release properties of the coated isomalt based cores are similar to the sucrose based pellet cores and show higher dissolution rates compared to the MCC cores [9].

The aim of the present study was to track and compare the simultaneous release of the active ingredient and inert core material from polymer coated drug layered pellets to characterize the influence of the core material.

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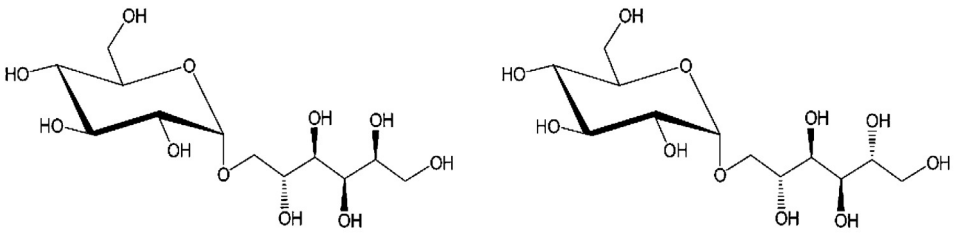

6-O-α-D-Glucopyranosyl-D-sorbitol (1,6-GPS)

1-O-α-D-Glucopyranosyl-D-mannitol dihydrate (1,1-GPM)

Fig. 1. Chemical structure of isomalt.

2. Materials and methods

2.1. Materials

Diclofenac sodium (M_w = 318, Sigma-Aldrich Chemie GmbH, Germany) was applied as model drug. Isomalt pellet core [1:1 mixture of 1-*O*-α-D-glucopyranosyl-D-mannitol (GPM) dihydrate and 6-*O*-α-D-glucopyranosyl-D-sorbitol (GPS); structures in Fig. 1] type galenIQ™ 980 was supplied by the manufacturer (BENEO-Palatinit GmbH, Germany). Hydroxypropyl methylcellulose (HPMC, Pharmacoat® 606, Shin-Etsu Chemical Ltd., Japan) was applied as binder for the drug layering process. An aqueous dispersion of polyvinyl acetate (PVAc based dispersion; Kollicoat® SR 30 D, BASF AG, Germany) was the film forming polymer. 1.2-Propylene glycol (Fluka Chemie, Switzerland) served as plasticizer.

2.2. Preparation of coated pellets

2.2.1. Drug layering of starter cores

Diclofenac sodium loaded pellets (5% w/w drug loading) were prepared by layering the drug-binder solution onto the inert cores (batch size: 200 g) using a fluidized bed coater (Aeromatic Strea I. type, Aeromatic-Fielder AG, Switzerland). The drug (15 g) was dissolved in 285 g of a 2.105% w/w HPMC aqueous dispersion. During the layering process the dispersion was stirred and kept at a constant temperature of 55–60 °C to keep the diclofenac sodium in solution. The layering conditions were: inlet air temperature:

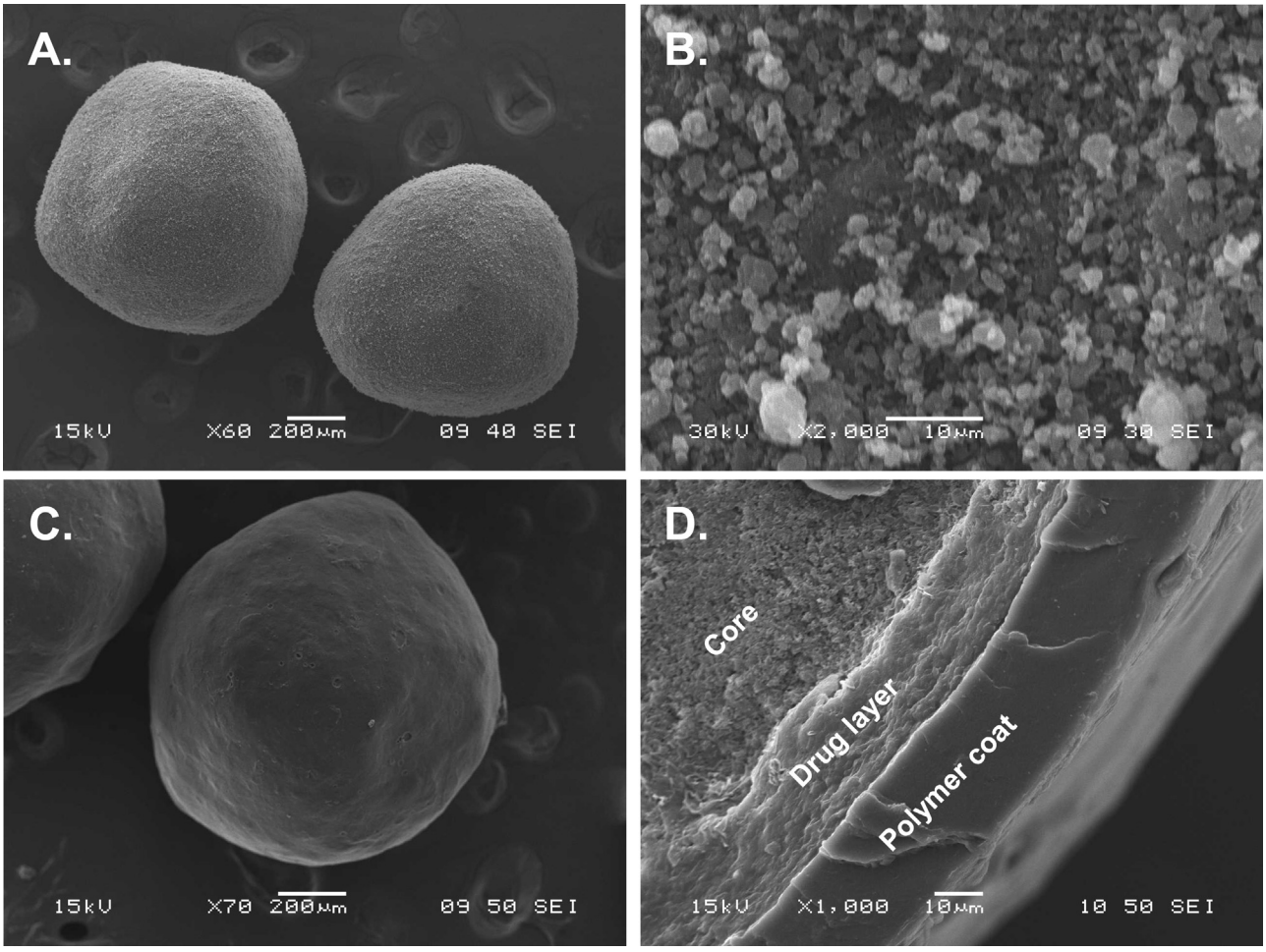

Fig. 2. Scanning electron microscopic images of pellets based on isomalt ((A) and (B) inert core; (C) and (D) drug loaded pellet, coated with PVAc at 15% coating level).